

AD \_\_\_\_\_

Award Number: W81XWH-08-2-0075

TITLE: Prazosin for Treatment of Patients With PTSD and Comorbid Alcohol Dependence

PRINCIPAL INVESTIGATOR: Ismene A. Petrakis, M.D.

CONTRACTING ORGANIZATION: Yale University  
New Haven, CT 06520

REPORT DATE: July 2011

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

<b>REPORT DOCUMENTATION PAGE</b>				<i>Form Approved</i> <b>OMB No. 0704-0188</b>	
<small>Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. <b>PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</b></small>					
<b>1. REPORT DATE (DD-MM-YYYY)</b> July 2013		<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED (From - To)</b> 1 July 2012 - 30 June 2013	
<b>4. TITLE AND SUBTITLE</b> Prazosin for Treatment of Patients With PTSD and Comorbid Alcohol Dependence				<b>5a. CONTRACT NUMBER</b>	
				<b>5b. GRANT NUMBER</b> W81XWH-08-2-0075	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b> Ismene Petrakis, M.D. Elizabeth Ralevski, Ph.D. E-Mail: ismene.petrakis@yale.edu				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b> Yale University New Haven, CT 06520				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Please see next page.					
<b>15. SUBJECT TERMS</b> Please see next page.					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>	<b>18. NUMBER OF PAGES</b>	<b>19a. NAME OF RESPONSIBLE PERSON</b>
<b>a. REPORT</b> U	<b>b. ABSTRACT</b> U	<b>c. THIS PAGE</b> U			<b>19b. TELEPHONE NUMBER (include area code)</b>
			UU	8	

#### 14. ABSTRACT

**Background:** There is a high rate of comorbidity with alcohol dependence (AD) and post traumatic stress disorder (PTSD). The rates of PTSD among individuals with AD are at least twice as high as those in the general population. In addition, alcohol dependence is the most common comorbid condition in men with PTSD. Despite this, little is known about how to best treat individuals with comorbid AD and PTSD. The use of an alpha-1 adrenergic receptor antagonist represents a novel approach to treatment that may target symptoms of both AD and PTSD. There is evidence of common neurobiological mechanisms that underlie both AD and PTSD. Prazosin is an alpha-1 adrenergic receptor antagonist that has been used successfully in the treatment of trauma nightmares and sleep disturbance in combat veterans with PTSD, and alcohol dependence.

**Objective:** The objective of this study is to evaluate the efficacy of prazosin (16mg) versus placebo in reducing alcohol consumption and decreasing symptoms of PTSD in patients with comorbid AD and PTSD. **Methods:** One hundred and twenty participants with a current diagnosis of AD and PTSD will be enrolled in a 13-week trial. They will be assigned, in a double-blind fashion, to either prazosin or placebo.

**Findings:** No findings are yet available for this study. **Significance:** This project will be the first to compare prazosin to placebo as effective treatments for reducing alcohol consumption and PTSD symptoms in patients with both AD and PTSD.

#### 15. SUBJECT TERMS

PTSD, alcohol dependence, treatment, Prazosin

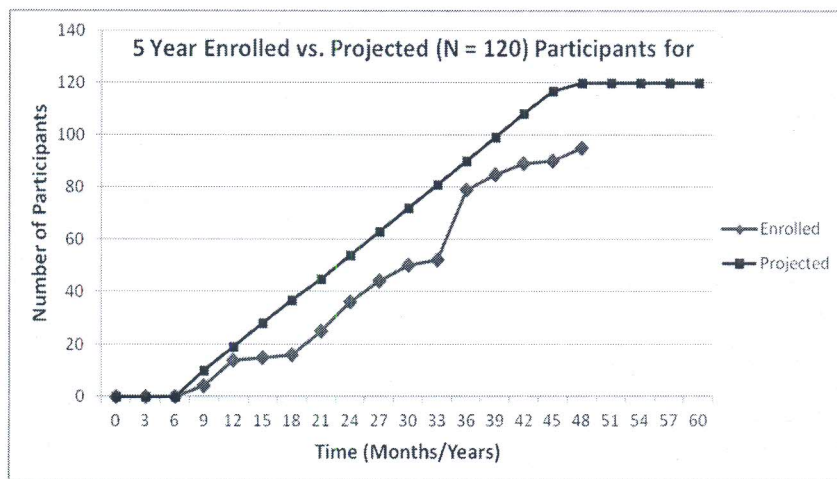
## TABLE OF CONTENTS

	Page
Introduction .....	3
Body.....	3
Key Research Accomplishments.....	4
Reportable Outcomes.....	4
Conclusion.....	5
References.....	6
Appendices.....	6

**INTRODUCTION:** The objective of this research is to evaluate the efficacy of Prazosin 16mg versus placebo in reducing alcohol consumption and decreasing symptoms of PTSD in patients with comorbid AD and PTSD. We hypothesize that Prazosin will significantly reduce the number of drinking days and reduce the symptoms of PTSD compared to placebo in patients with AD and PTSD. This is a double-blind, multi-site, randomized, 13-week, treatment trial. The recruitment for this study is planned for 4 years and a 1 year no cost extension (NCE) has now been approved.

**BODY:** This report covers the period of the first no-cost extension. Our goals for this period were to: continue subject recruitment, develop and implement new avenue for recruitment, create new liaisons for recruitment, and follow patients already recruited in the study. The goals for this year have been accomplished regarding continuous recruitment as well as initiation and implementation of new recruitment strategies. However, our goal to recruit a total of 120 subjects has not been reached. Below we provide graphical representation of our recruitment to date in relationship to the goals we outlined in our statement of work. Our recruitment is progressing, and we have developed and implemented a number of strategies to increase recruitment in the past year. At the West Haven site, we have allocated resources for newspaper advertisement, and we created new liaisons in the community. Our recruitment has improved but in order to reach our recruitment goal we need to recruit more subjects into the study.

The recruitment at West Haven has been slower than predicted and what we are experiencing at our Bedford site. We believe that the differences in site explain, in part, the differences in recruitment. For example, Bedford has a residential program that allows for more stable patients to be in the potential subject pool. West Haven is a more acute setting so while a great number of patients have signed consent (n=20), we have only randomized 9 participants. Nevertheless we are trying to address this shortage. In the past few months we have implemented a number of new strategies to increase recruitment: 1) one staff member is actively recruiting participants from the Newington VA (an affiliate of West Haven VA). Those participants can be seen at Newington or since there is a scheduled daily shuttle several times per day between the two VAs study visits can be arranged at West Haven VA as well; 2) we have implemented daily recruitment to our Emergency Room to identify potential subjects; 3) we most recently have begun to evaluate all patients who are seen by our Integrated Psychiatric Care clinic (psychiatric care embedded in a primary care setting).



Included in this report is a table that outlines our recruitment – at both sites - to date.

Site	# Ss that have signed consent	# Ss enrolled	Ratio of Ss to target
West Haven	123	40	40/72
Bedford	88	55	55/60

**KEY RESEARCH ACCOMPLISHMENTS:** This study is ongoing and no statistical analysis of the data has been conducted to date.

**REPORTABLE OUTCOMES:** The PI gave a presentation at the American Psychiatric Association Annual meeting on the comorbidity of PTSD and alcohol dependence in 2009. An abstract was also submitted for the Military Health Research Forum. A poster was presented at the Research Society of Alcoholism meeting in Atlanta, GA (June, 2011) comparing demographic characteristics of patients with dual diagnosis of AD and PTSD (from this study) and patients with only AD diagnosis (who had enrolled in another pharmacotherapy study). Analysis of the data for this poster revealed that the two groups were very similar in terms of their demographic characteristics. There were no differences in age, gender, marital status, education, employment status, or yearly income. There were significant differences in ethnicity ( $p=0.017$ ); larger sample of those with AD alone considered themselves “White” while a larger sample of those with PTSD and AD considered themselves “Puerto Rican”. Also all participants (100%) with PTSD and AD were veterans while the sample of participants with AD alone consisted of 68% veteran population.

There were significant differences in personality measures based on the NE, where the comorbid group had higher levels of impulsivity and neuroticism than the non-comorbid group. Also the comorbid sample had higher rates of psychiatric symptoms and psychiatric distress than the non-comorbid sample. Interestingly, the comorbid group had different alcohol consumption patterns. They reported lower levels of drinking as measured by drinking days and heavy drinking days but reported higher levels of consequences from their alcohol use based on the ADS.

At the Research Society of Alcoholism meeting in San Francisco, CA (June, 2012) some preliminary data was presented that evaluated the relationship between stress and drinking. The data come from a laboratory study designed as a companion to this treatment trial. The laboratory study design consists of II phases. *In Phase I*, all subjects participate in a **laboratory session I** to determine their reactivity to stress. Stress reactivity in the laboratory is generated using: a personalized trauma-related stressor, a personalized non-trauma related stressor and a neutral stressor, presented randomly. Outcome measures include self-reported measures of alcohol craving and anxiety. *Subjects are subsequently randomized into the clinical trial within a week of the laboratory session.* *In Phase II*, subjects participate in **laboratory session II, a repeat of session I**. This second session occurs after at least 6 weeks of medication treatment

and while participants are still receiving prazosin or placebo. The main outcome measures for the laboratory study include measures of alcohol craving and anxiety.

The findings to date indicate that: **A)** Subjective levels of craving and anxiety significantly increase after the trauma and stress session, but not the neutral session; there was a significantly higher level of craving and anxiety reported after the trauma imagery when compared to both stress and neutral imagery. **B)** Changes in peak stress response was significantly correlated with changes in heavy drinking – the bigger the change in stress response the bigger the change in heavy drinking. **C)** Individuals were characterized as high stress responders (HSR) vs. low stress responders (LSR). HSR's had an overall smaller change in their drinking behavior compared to LSR's and this change was mediated by medication treatment. Specifically, a prazosin effect on alcohol drinking was the strongest in the LSR group.

At the Research Society of Alcoholism meeting in Orlando, Florida (June, 2013) additional data was presented on the relationship between stress and drinking. We compared veterans diagnosed with PTSD+AD to veterans and non-veterans with AD diagnosis on their reactions to stressful stimuli. The data showed that those with dual diagnosis had significantly stronger reactions to stress than those with diagnosis of AD alone.

A manuscript entitled "Characteristics and drinking patterns of veterans with alcohol dependence with and without post traumatic stress disorder" is currently under review in the journal of "Addictive Disorders". The paper explored differences in the pretreatment characteristics of veterans with alcohol dependence alone compared to those with co-occurring alcohol dependence and posttraumatic stress disorder. Veterans were recruited to participate in two different treatment studies and baseline characteristics were compared. Those with co-occurring illnesses demonstrated significantly higher pre-treatment pathology across all psychopathological domains. While those with alcohol dependence alone averaged more days of drinking, and had more heavy drinking days, while those with co-occurring illnesses reported more drinking-related symptoms. Within the PTSD group, combat exposure was associated with increased drinking independent, of the severity of PTSD symptoms. This study underscores the importance of screening for comorbidity in clinical treatment settings, and for collecting detailed drinking histories and assessment of psychiatric symptoms across all domains of psychopathology.

**CONCLUSION:** To date, no statistical analysis has been conducted on the entire sample. We can report that to date, medication has been well tolerated. During this reporting period there was one serious and unexpected adverse event occurring at our Bedford site. The participant received study medication with another person's name and address on the blister pack. Veteran Subject "A" reported taking 10 doses (5 days) of the study medication before noticing this. The research team discovered that the medication was intended for Veteran Subject "B." Both Subjects were in week 10 of the research study. Subject "A" was evaluated by the research nurse and found to be medically stable. He/she was either receiving placebo twice a day or prazosin 8mg twice a day. He/she reported feeling well and did not notice any differences in his/her physical or mental status the previous week. The blind was broken for both Subjects by one member of the study team as directed by the Chief of MH to assess what research medication subject "A" was randomized to and what research medication was taken incorrectly at week 10 in order to determine further action required for the continued health of Subject "A". Both

Subjects and the other members of the research team remain blinded. The Bedford IRB determined this event was serious, unanticipated, and related to study participation.

**REFERENCES:** None, to date.

**APPENDICES:** None, to date.